REMARKS

Claims 1, 20-22, 24, 45, 57-59, 61, 62, 67, and 77 are pending, and stand rejected.

Applicants thank the Examiner for withdrawal of prior 35 U.S.C. 112 new matter rejection, rejections as stated at page 2 of the present Office Action (hereinafter "OA"), wherein the Examiner cites support in Figure 19 and at paragraph [0051].

Applicants acknowledge the Examiner's new and modified grounds of rejection as addressed in the OA.

Claims 1, 2, 45, 59, 62, and 77 have been amended herein.

Applicants respectfully contend that the presently-amended claims are allowable.

Rejections under 35 U.S.C. § 112, second paragraph

A. The Examiner has rejected claims 1, 20-22, 24, 45, 57-59, 61, 62, 67, and 77 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in view of recitation of "consisting essentially of."

Applicants have responsively amended claims 1, 2, 45, 59, 62, and 77 by deleting the work "essentially" to obviate this rejection.

B. The Examiner has rejected claims 1, 20-22, 24, 45, 57-59, 61, 62, 67, and 77 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in view of the lack of recitation of how the method affords the prediction of responsiveness to therapeutic treatment.

Applicants have amended claims 1, 45, and 62 as constructively suggested by the Examiner to obviate this rejection.

Applicants, therefore, respectfully request withdrawal of these rejections.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1, 20-22, 24, 45, 57-59, 61, 62, 67, and 77 under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient enablement, for reasons stated in the

OA.

The Examiner states (page 7) that "the claims encompass methods which predict responsiveness to ***any*** type of adjuvant therapy that targets the estrogen receptor pathway or is involved in estrogen metabolism, production or secretion. Thereby, the claims encompass determining responsiveness to a very wide range of drugs (antisense drugs, ribozymes, antibody therapy, organic and inorganic compounds), which differ in their structure and mechanism of action" (emphasis added).

As an initial matter, claims 1, 45, and 62 have been amended, as suggested by the Examiner, to recite "a method for determining if a human subject having an estrogen receptor-positive breast cancer has a high risk of relapse or a low risk of relapse following adjuvant..." The claims, therefore, do not recite predicting *any* type of *responsiveness* to any type of adjuvant therapy...."

Additionally Applicants have herein amended claims 1, 45, and 62 to recite "drugs that inhibit-the estrogen receptor pathway of breast cancer cells," to clarify that the nature of the adjuvant therapy is administration of drugs that inhibit or antagonize the estrogen receptor pathway of breast cancer cells. Support for the amendment is found at page 5, discussing antiestrogenic drugs (i.e., tamoxifen, SERMs, etc.). It is clear from the specification, as recognized in the art, that drugs that inhibit or antagonize the estrogen receptor pathway, including those that "reduce serum estrogen levels" would reasonably be within the scope of Applicants' conception, because, like the exemplary antiestrogenic drug Tamoxifen, they would expected to inhibit or antagonize the estrogen receptor pathway of breast cancer cells expressing estrogen receptor.

The Examiner further states (page 7) that the claims also include "methods in which ***any*** biological sample from a subject is analyzed for CpG methylation in a PITX2 gene sequence."

Applicants have amended claims 1, 45, and 62 to recite "a biological sample comprising breast cancer cell genomic DNA from the subject" to clarify that the biological sample comprises genomic DNA of breast cancer cells.

The Examiner further states (page 8) that the claims "include analyzing the methylation status of any one or more CpG dinucleotides in the 6343bp sequence of SEQ ID NO: 83."

The Examiner further states (page 8) that "the claims broadly recite determining the genomic DNA methylation status 'wherein predicting responsiveness of the subject to the therapy is afforded.' While the claims recite the hypomethylation is indicative for a low risk for relapse while hypermethylation is indicative for a high risk for relapse, the claims do not recite how the method affords the prediction of responsiveness. The claims do not set forth a relationship between relapse and responsiveness or clarify how the method accomplishes the goal of predicting responsiveness."

As discussed above, Applicants have amended claims amended claims 1, 45, and 62 to recite "a method for determining if a human subject having an estrogen receptor-positive breast cancer has a high risk of relapse or a low risk of relapse following adjuvant" and "wherein hypomethylation of SEQ ID NO:83 or the complement thereof is indicative of a low risk for relapse following adjuvant therapeutic treatment and hypermethylation of SEQ ID NO:83 or the complement thereof is indicative of a high risk for relapse following adjuvant therapeutic treatment." The claims, therefore, clearly recite how the method accomplishes the goal, and do not recite predicting *any* type of *responsiveness* to any type of adjuvant therapy…."

The Examiner states (page 10) that the nature of the biological art is unpredictable.

The Examiner (page 11) states that "with respect to the examples provided in the specification, the information regarding the characterization of the subjects (type, stage etc of the disorder), drug used for treatment, and criteria for defining responders versus non-responders is unclear."

Applicants respectfully disagree. As stated in the specification at page 15, in adjuvant setting embodiments stage 1 to 3 breast carcinomas are typically used. This is distinguished from a second "metastatic" embodiment (later stage breast carcinomas). As stated in the specification at page 48, Applicants show a method that allows for predicting "the likelihood of therapy response in patients with ER-positive *advanced breast cancer* treated with Tamoxifen therapy."

Example 1 states that DNA samples were extracted using "samples from 200 *patients*." It is readily apparent, therefore, to one of skill in the art that these patients would be breast cancer patients, and it would be reasonably assumed that they would be female breast cancer patients. The Examiner, moreover, acknowledges that Example 1 (e.g., data set 1) shows responders or non-responders to Tamoxifen as an adjuvant therapy following surgery.

Applicants further point out that the criteria for defining responders versus non-responders is given in the specification at pages 32-33 (discussion of Figure 1). Disease free survival is discussed in relation to Figure 14 at page 34. In particular, the specification at page 43 describes that subject with a disease free survival of less than 36 months were classified as non-responders and subjects with a disease free survival of greater than 60 months were classified at responders.

The Examiner states (page 12) that figures 5 and 6 "do not identify the particular nucleotide position of the CpGs within the PITX2 gene or the amplified fragment of the PITX2 gene. Thereby, it cannot be ascertained which particular CpGs show a difference in methylation status between responders and non-responders."

Applicants point out that the description of Figures 5 and 6 refers to Example 1 data set 1. According to Example 1 data set 1 p40 primers 1055 and 1056 are used for amplifying the PITX2 amplificate which is then hybridized to the PITX2 detection oligos of Table 2 (see "Bisulfite treatment and mPCR" and "Hybridisation"). Thus the oligos of Table 2 (2023-2028) explicitly define all the CpG positions of the amplificate. From comparing the sequence of the oligos it becomes clear that:

(a) they form 3 pairs: 2023+2024; 2025+2026; 2027+2028;

(b) each oligo covers 2 CpG positions

(c) oligos 2023, 2025, and 2027 detect the methylated Cs, respectively; and

(d) oligos 2024, 2026, and 2028 detect the un-methylated Cs, respectively.

Applicants further point out the specification teaches that the amplicon and these CpG positions are within a CpG island wherein co-methylation would be reasonably be expected, and is thus inherent in the design of the detection oligos as both CpG positions within each oligo are

designed to detect coordinate methylation, and so effective hybridization of any given oligo would not be possible absent co-methylation. Therefore, the methylation data of Figures 5 and 6 inherently corroborate that co-methylation is occurring within the amplicon, and in this sense one of skill in the art would understand that the specification teaches at least that any CpG of the detection oligos can be used, and that this would reasonably be expected to extend across the amplicon of the CpG island. Applicants further point out that given the explicit disclosure of exemplary CpG positions (e.g., within the PITX2 detection oligos and amplicon), one of ordinary skill in the art could readily determine without undue effort (i.e., within a few days or a week, given array-based methods available at the time of filing) whether any other particular CpG position within the claimed PITX2 sequence was coordinately methylated with CpGs of the explicitly disclosed detection oligos, and therefore readily practice the invention commensurate with the claimed scope.

The Examiner states (page 12) that "The specification at pages 44-45 discusses the results associated with a 'Data set 2: Adjuvant setting.' It is stated that every CpG was put into a Cox proportional hazard model with predictive factors of N-stage and tumor size. The specification states that the best marker was the PITX2 gene. However, the specification fails to state what PITX2 is a marker of. For example, is PITX2 the 'best marker' of survival, N-stage, tumor size, response to treatment?"

Applicants point out that Data set 2 obviously relates to the best markers for survival time (i.e., responders vs non-responders) in the adjuvant setting..

The Examiner states that "it is also stated that oligonucleotide 3522:2087 gives information about survival time independent of nStage. However, the specification does not characterize the identity of oligonucleotide 3522:2087. Also, in this example, the number of patients analyzed is not provided, nor are the patients characterized with respect to their disorder, treatment, age, sex etc. Moreover, survival time, N-stage and tumor size are considered to be prognostic factors and are not equivalent to determining the responsiveness to therapy."

Applicants confirm that oligonucleotide number 3522:2087 refers to detection

oligonucleotide SEQ ID NOS:2027 and 2028, which were disclosed in the originally filed Sequence Listing.

Applicants additionally point out, as explained above, that responsiveness to therapy is, in fact, determined based on survival time.

The Examiner states (pages 45-46) that "at page 45, the specification discusses a "Data set 4: Metastatic setting." While the subjects are characterized as being treated with tamoxifen, the subjects are not characterized with respect to their disorder. It is stated that individual CpGs measured were combined for each gene. However, the region of the PITX2 gene analyzed, and thereby the CpGs analyzed is not clearly stated."

Applicants disagree, however, as stated above, Applicants have at any rate amended the claims to cover the adjuvant setting.

The Examiner states (pages 13-14) that "the specification does not clearly characterize the identity of the PITX2 amplification products that were analyzed" and whether the adjuvant treatment is tamoxifen or some other unspecified adjuvant therapy.

Applicants contend that it is clear from the specification that the adjuvant setting is that of exemplary Tamoxifen adjuvant therapy, and that the amplicon is the 408 bp region defined by primers 1056 and 1055 of Table 1 at page 54.

Applicants point out, with respect to the Examiner's contentions (pages 14-15) regarding the findings of Martens were discussed by Nimmrich et al. (Breast Cancer Research and Treatment. 2008. 111:429-437) (hereinafter "Nimmrich"), that Nimmrich refers to metastatic breast cancer and thus not to an adjuvant setting as presently claimed. Likewise, Martens refers to a metastatic setting (e.g. page 4101, left column, first paragraph and last paragraph, page 4102, right column, first paragraph). Applicants have amended the claims to recite application to the adjuvant setting.

The Examiner states (page 17) that "the claims do not require any type of comparison step with a control, non-cancer or non-responsive sample, and thereby include methods in which the presence or absence of methylation at a single CpG is detected as predictive of response."

Applicants point out that the specification at Example 1, page 42, under "class prediction by supervised learning", there was an initial learning phase, wherein the status responder/non-responder was known for samples, and it was determined that samples from responders are more highly methylated relative to samples from non-responders. PITX2 CpGs are thus differentially methylated between the responder and non-responder classes.

With respect to any alleged requirement for undue experimentation, Applicants respectfully request withdrawal of this rejection based on the present limiting claim amendments, and in view of Applicants' rebuttal remarks already of record with respect to the availability of high-throughput methylation assays, and the nature of co-methylation that occurs within the PITX2 gene and its regulatory sequences, Applicants contend that while Applicants' specification and working Examples do not explicitly include analysis of each and every CpG position within the PITX2 gene and/or its regulatory elements, Applicants' method claims are nonetheless entitled to a broad scope with respect to the PITX2 gene limitation. A contrary conclusion would not comport with U.S. patent law on enablement.

Specifically, to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without *undue* experimentation (*Atlas Powder Co.*), where this requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim" (*In re Anderson*). A patentee is not only entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities (*Id*). Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it" (*In re Grimme*). There is, therefore, no requirement for disclosure of every species within a genus. Applicants are entitled to claims that are

commensurate in scope not only with what Applicants have specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicants have disclosed.

Applicants point out that under U.S. patent law, a considerable amount of experimentation is permissible, particularly if it is routine experimentation. As appreciated by the Examiner, the amount of experimentation that is permissible depends upon a number of factors (A, claim scope; B, nature of invention; C, state of the prior art; D, level of skill in the art; E, level of predictability; F, amount of direction provided; G, working examples; and H, quantity of experimentation required) as discussed herein above. The Examiner has offered insufficient evidence to support that any alleged amount of experimentation is other than rapid, high-throughput and routine.

With respect to these factors in the present case, the Examiner appreciates that the level of skill in the art is very high (as evidenced by the Examiner's own cited art references), and given the nature of the invention in terms of the realities of high-throughput methylation assays and co-methylation within the PITX2 gene and its regulatory sequences, Applicants contend that a *prima facie* case of insufficient enablement cannot reasonably be supported under U.S. Patent law, because under the proper analysis of *all* Wands factors, any amount of experimentation required to practice the invention as presently claimed would in fact be merely routine, and insufficient to support the Examiner's allegation of *undue* experimentation. Improper limitation of Applicants' invention to particular exemplary preferred regions within the PITX2 gene is not only impermissible under U.S. patent law in view of the present facts, but would also be unjustifiable—in that a person of ordinary skill in the art could, using routine, efficient methods readily identify and select alternate diagnostic CpG positions within the PITX2 gene and its regulatory sequences but outside Applicants' exemplary preferred regions, thus effectively eviscerating Applicants' claimed invention.

In response to the Examiner's concerns relating to "*any* region of the PITX2 gene" Applicants maintain Applicants' *traverse* of record, and respectfully contend that the Examiner's position regarding the standard for sufficiency of enablement in the context of potential

inoperative embodiments is not reasonably supportable under U.S. patent law jurisprudence or the MPEP provision cited by the Examiner.

Improper application of MPEP 2164.08(b)

As an initial matter, MPEP 2164.08(b) is reproduced below:

2164.08(b) Inoperative Subject Matter

The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).

Although, typically, inoperative embodiments are excluded by language in a claim (e.g., preamble), the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. *In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). However, claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

(emphasis added). Clearly, consistent with the case law cited by Applicants in the prosecution record, the applicable standard (underlined above) is "The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art."

By contrast, the Examiner, at pages 28-29 of the OA, states that:

> "Applicants arguments do not establish that the results of performing such assays would be ***predictable*** and would allow the artisan to practice a method of predicting any type of response to any type of adjuvant therapy in a breast cancer patient by determining the methylation status of any CpG in a PITX2 gene sequence of SEQ ID NO: 83 obtained from any tissue or fluid sample of an estrogen receptor positive breast cancer patient."

(emphasis added).

As is readily apparent, the proper standard is NOT whether the "specification has guidance to determine which CpGs are correlative without experimentation," as urged by the Examiner. Rather, the standard is whether any such required experimentation would be undue.

Additionally, whether an amount of experimentation is undue is NOT determined based on whether the artisan would have a "predictable determination" as urged by the Examiner. No such ability to *predict* an operable or inoperable embodiment is implicated under the standard. Rather, the standard is whether the amount of experimentation required would be considered undue in the relevant art (e.g., no more that is normally required).

There is no requirement that the artisan be able to *conceive* of which embodiments are inoperable or operable, as urged by the Examiner. **Rather, the standard is whether any such required experimentation would be undue**.

Applicants are entitled to claims that are commensurate in scope not only with what Applicants have specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicants have disclosed.

In view of the present claim amendments, Applicants respectfully contend that the currently amended claim scope is commensurate with the teachings of the specification, and request withdrawal of the Examiner's rejection based on lack of sufficient enablement.

Obviousness-type Double Patenting Rejection

The Examiner has *provisionally* rejected claims 1, 20-22, 24, 45, 57-59, 61, 62, 67, and 77,

on the grounds of nonstatutory obviousness-type double patenting, as being unpatentable over claims 1-4, 6-7, and 11-16 of Applicants' copending Application No. 10/582,705 in view of Berlin et al. (WO 02/77272, 03 October 2002) (hereinafter "Berlin").

Applicants respectfully traverse this rejection based on the fact that in view of the prior art (including that specifically cited and discussed by the Examiner in the OA), no *prima facie* case of obviousness can be supported.

Specifically, Applicants have previously amended the claims to recite "complements thereof," in place of "sequences complementary thereto," such that the Examiner's underlying reliance on "complementarity" to SEQ ID NO:23 of '705 is not reasonably supported.

Additionally, the pending application claims PITX2 as a treatment response predictive marker, whereas Applicants' Serial No. 10/582,705 ('078US0, P190US) claims PITX2 as prognostic marker, such that the two application claim distinct inventions. Moreover, the teaching of Berlin, as appreciated by the Examiner, relate to hematopoietic disorders, and thus does not support the Examiner's obviousness contention.

In view of the present claim amendments and arguments, Applicants respectfully request withdrawal of this provisional rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request entry of the present Response and Amendment and allowance of all claims as provided herein above. The Examiner is encouraged to phone Applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

Davis Wright Tremaine LLP
1201 Third Avenue, Suite 2200
Seattle, Washington 98101-3045
Telephone: 206-757-8023
Facsimile: 206-757-7023

Respectfully submitted,
John Foekens et al.
Davis Wright Tremaine LLP

/Barry L. Davison, Ph.D., J.D./
Barry L. Davison, Ph.D., J.D.
Attorney for Applicants
Registration No. 47,309